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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/031,947 | 05/15/2002 | Atef Gayed | MAR618/4-5(A)US | 8100 |

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| EXAMINER | |
|---|---|
| SCHNIZER, HOLLY G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/031,947 | GAYED, ATEF | |
| | Examiner | Art Unit | |
| | Holly Schnizer | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *p. 2 of 1/7/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Claims*

The Amendment and Response filed 10/1/04 has been entered and considered. Claims 1- 72 are pending and have been considered in this Office Action.

### *Information Disclosure Statement*

Reference D6 of the Information Disclosure Statement filed January 7, 2003 was provided with the Response filed 10/1/04. However, the reference was not filed with a new Form 1449 and the appropriate fee. Therefore, the reference has been placed in the file but is not of record. The examiner also notes that the page numbering and date of citation D6 of the IDS filed 1/7/03 does not match the reference provided. If Applicant wishes to cite Miyake et al. in a future Form 1449, the citation should be corrected to match the reference.

References D9 and D10 of the IDS filed December 15, 2003 have not been received and therefore have not been considered (see OA mailed 5/26/04 under Information Disclosure Statement).

### *Rejections Withdrawn*

The rejection of Claims 50-51 under 35 U.S.C. 112, second paragraph is withdrawn in light of the amendment to the claim.

***Rejections Maintained***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

***Claim Rejections - 35 USC § 112***

Claims 4-15 and 23-33 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons cited in the Office Action mailed 5/26/04—they are unclear as to whether the percentage is by weight or by molar concentration.

Applicants argue that the Specification discusses that the percentages are a weight/volume measure and therefore no amendment of the claims is necessary.

This argument has been considered but is not deemed persuasive. The Specification does not define that the percentages are always a weight/volume measure and while the claims are read in light of the Specification, the Specification is not read into the claims. While claims must be "given the broadest reasonable interpretation consistent with the specification", "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from `reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." *In re Prater* , 162 USPQ 541, 550 -51 (CCPA 1969). This is impermissible importation of subject matter from the specification into the claim. Thus, as stated in the previous

Office action, the rejection is maintained because the claims are unclear as to whether the percentage is by weight or by molar concentration. Correction is required.

***Claim Rejections - 35 USC § 102***

Claims 20, 23-27, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Kakimoto et al. for the reasons cited in the previous Office Action (mailed 5/26/04).

Applicants argue that Kakimoto et al. does not disclose the same use of benzethonium chloride as in the present invention and that Kakimoto et al. does not make reference to erythropoietin.

This argument has been considered but is not deemed persuasive for the following reasons. The Kakimoto et al. composition contains all of the components of the claimed composition and is therefore patentably indistinguishable from that of the claimed composition. The rejected claims do not require the presence of erythropoietin in the composition but only require that the claimed composition have an intended use as a carrier of erythropoietin. As stated in the previous Office Action (p. 4 of Action mailed 5826/04), even though the composition is to be used as a carrier of erythropoietin, without a recitation that erythropoietin is part of the composition, the claims have been interpreted to encompass compositions containing benzethonium chloride alone. Moreover, the intended use of the composition disclosed in Kakimoto et al. is immaterial to the determination of anticipation unless that intended use changes the structure or components of the composition such the composition is patentably

distinct from the claims. At present, the Kakimoto et al. composition contains the identical components as the present invention—benzethonium chloride. Thus, the composition of Kakimoto et al. is patentably indistinguishable from the composition of the claims and the rejection is maintained.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Nomura et al. for the reasons cited in the previous Office Action (mailed 5/26/04).

Applicants argue that Nomura et al. does not mention using benzethonium chloride as a preservative and that the reference does not discuss or provide any indication whether an amount of benzethonium chloride would have any antimicrobial effect and that it is unclear what concentration of benzethonium chloride would be necessary to function as an effective surfactant or would be an effective antimicrobial since benzethonium chloride is not used in any examples.

This argument has been considered but is not deemed persuasive. The claimed composition contains erythropoietin and an amount of benzethonium chloride effective to inhibit microbial growth. The question at hand is not whether or not Nomura et al. knew that the concentrations of benzethonium chloride disclosed would inhibit bacterial growth but whether or not the Nomura et al. composition is patentably distinguishable from the claimed composition. Nomura et al. teaches that the composition contains between 0.1 and 1000 parts by weight benzethonium chloride to one part by weight EPO. Absent evidence to the contrary, this concentration of benzethonium chloride would be effective to inhibit microbial growth. Therefore, the Nomura et al. composition

is patentably indistinguishable from that of Claim 1 and therefore the rejection is maintained.

***Claim Rejections - 35 USC § 103***

Claims 1, 4, 5, 7, 8, 16-20, 23, 24, 26, 27, 34-35, 50-54, 57-61, and 69-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strickland et al. in view of Uda et al. and Sandeep et al.

Applicants argue that Strickland explicitly states that the use of preservatives with other proteins does not suggest any particular preserved formulation for erythropoietin. Applicants further contend that Strickland et al. dos not suggest that benzethonium chloride can be substituted for benzalkonium chloride and that because of this Strickland et al. teaches away from such a substitution. In addition, Applicants argue that Uda never identifies any particular combination of peptides with benzethonium chloride that would be effective and neither EPO or benzethonium chloride are used in any examples.

These arguments have been considered but are not deemed persuasive for the following reasons. First, it does not appear that the quoted statement attributed to Strickland et al. in Applicants arguments is stated in the reference (the Strickland et al. reference did not make the statement). Second, In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800

F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). While Strickland et al. does not teach the use of benzethonium chloride, as stated in the previous Office Action Uda et al. and Sandeep et al. do make such a suggestion. The selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness (see MPEP 2144.07). In the present case, Uda et al. and Sandeep et al. provide evidence that benzethonium chloride was a well-known antimicrobial preservative. Strickland et al. provides evidence that using antimicrobial preservatives in erythropoietin multi-dose solutions was well known at the time of the invention. Both benzalkonium chloride (disclosed as an example of a preservative to use in erythropoietin solutions in Strickland et al.) and benzethonium chloride were considered functionally equivalent, as evidenced by Uda et al. Thus, the rejection is maintained.

Claims 2-3, 6, 9-15, 21-22, 25, 28-33, 36-49, 55-56, and 62-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strickland et al., Uda et al., and Sandeep et al., as applied to claims 1, 4, 5, 7, 8, 16-20, 23, 24, 26, 27, 34-35, 50-54, 57-61, and 69-72 above, and further in view of Hyman et al.

Applicants argue that nothing in Hyman or any other cited reference suggests that the synergistic effect of combining 9-aminoacridine hydrochloride with benzethonium chloride would be achieved with any other combination of preservatives. Further, Applicants argue that there is nothing in Hyman et al. suggesting that such a combination could be used to create pharmaceutical compositions.

These arguments have been considered but are not deemed persuasive for the following reasons. In response to applicant's arguments against Hyman et al. individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). With the teachings of the references as a whole in hand, it would have been obvious to one of ordinary skill in the art at the time of the invention to add a second preservative to a erythropoietin solution so that the concentration of each preservative could be reduced as taught in Hyman et al. As stated in the previous Office Action, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose (MPEP 2144.06). In the present case, benzethonium chloride, phenoxyethanol, and phenyl ethyl alcohol were all well-known preservatives at the time of the invention. Furthermore, Hyman et al. demonstrates that combining two preservatives (benzethonium chloride and 9-aminoacridine hydrochloride) results in a synergistic reaction that provides much greater inhibition to bacterial growth. Thus, the rejection is maintained.

Claims 1, 4-8, 16-19, 35, 38-42, and 50-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kakimoto et al. and Shimoda et al. and Uda et al. for reasons cited in the previous Office Action (mailed 5/26/04).

Applicants did not respond or provide any arguments to this rejection. Therefore, the rejection has been repeated as it appeared in the previous Office Action.

Shimoda et al. teaches that the adsorption of erythropoietin on the glass or plastic containers was a recognized problem in the art at the time of the invention (Col. 1). Shimoda et al. teaches a variety of additives that can be added to erythropoietin compositions to reduce the adsorption to the containers.

Shimoda et al. do not teach that benzethonium chloride can be used to prevent adsorption of erythropoietin to the walls of a container.

Kakimoto et al. teaches that adding 0.001% to 1% benzethonium chloride to pharmaceutical compositions prevents proteins from being adsorbed on the inner wall of the container that holds the composition (p. 6, line 10-p.7, line 19). Kakimoto et al. teaches that the methods disclosed therein can be used to prevent the effects against any peptide which tends to adsorb on container walls and is not limited to any protein or peptide (p. 6, lines 1-5).

Uda et al. provides evidence that at the time of the invention, those of ordinary skill in the art recognized that benzethonium chloride could be added to aqueous solutions as a preservative (Col. 6, lines 28-35).

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the composition disclosed in Shimoda et al. by adding benzethonium chloride to the erythropoietin composition, a known additive that would prevent protein adsorption on the wall of the container as taught in Kakimoto et al.. One of ordinary skill would have been motivated to choose benzethonium chloride over the additives taught

in Shimoda et al. because 1) benzethonium chloride appears to be more effective at lower concentrations than the additives disclosed in Shimoda et al. (compare Figs. 1-10 of Kakimoto et al. to the Table in Col. 4 of Shimoda et al.) and 2)benzethonium chloride has the added benefit of acting as a preservative as taught in Uda et al.

***Conclusions***

No Claims are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (571) 272-0958. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Holly Schnizer
December 21, 2004

JON WEBER
SUPERVISORY PATENT EXAMINER